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Recent developments in transplant-associated thrombotic microangiopathy

Tapani Ruutu
Clinical Research Institute, Helsinki University Hospital

Professor Tapani Ruutu, Helsinki University Hospital, Biomedicum 2C, POB 705, FIN-00029 HUS, Helsinki, Finland
Phone: +358 50 555 1279
Fax: +358 9 4717 1506
E-mail: tapani.ruutu@hus.fi

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Summary

Transplant-associated thrombotic microangiopathy (TA-TMA) is a relatively common complication of hematopoietic stem cell transplantation. The pathophysiology is complex, the central feature is endothelial injury. The role of complement activation in the pathophysiology has been increasingly recognized. The diagnostic procedures and interpretations vary considerably between centers, and aims at standardizing the criteria of this complication are important especially for study purposes. The therapy is improving, particularly due to the introduction of complement inhibitors. However, the indications and policy of administration of these drugs are not well established and need further study.

Keywords

Hemopoietic stem cell transplantation, thrombotic microangiopathy, diagnostic techniques, standardization, therapy, complement inhibitors.

Introduction

Transplant-associated thrombotic microangiopathy (TA-TMA) is a relatively common complication of hematopoietic stem cell transplantation. It belongs to the early endothelial damage syndromes together with veno-occlusive disease or sinusoidal obstruction syndrome of the liver, diffuse alveolar hemorrhage, engraftment syndrome and capillary leak syndrome. TA-TMA manifests itself as generalized microangiopathy causing organ injury particularly in the kidneys but also in other organs [1].

The reported incidences of TA-TMA have varied greatly, in allogeneic transplantation between 0 and 76 per cent [2, 3]. At the present time, the incidences of clinically significant TA-TMA may commonly be 5-10%, depending on several factors including patient material, transplantation methods and the diagnostic criteria used. In autologous transplantation the incidence is generally lower; incidence figures between 0 and 27% have been reported [2].

The pathophysiology of TA-TMA is complex [3]. The central feature is endothelial injury. Important etiological factors include pretransplant conditioning, calcineurin inhibitors, infections and graft-versus-host disease. The role of complement activation in the pathophysiology has been increasingly recognized.

TA-TMA differs from idiopathic acquired TTP in several respects. There is an absence of severe ADAMTS 13 deficiency, the spectrum of clinical symptoms is different, and, in contrast to idiopathic TTP, the response to plasmapheresis is usually poor.

Significant developments have taken place in recent years, both in the diagnosis, understanding of the pathophysiology, and the treatment of TA-TMA.

Diagnosis of TA-TMA

A large variety of diagnostic criteria have been used over the years [4]. Recently, three sets of criteria have been mainly used, those produced by the International Working Group [5], the American Bone Marrow Transplant Clinical Trials Network criteria [6], and the "overall TA-TMA" criteria by Cho et al [7]. The most important components of these definitions have been the presence of schistocytes, thrombocy-

topenia, anemia or increased need for red cell transfusions, increased lactate dehydrogenase (LDH) concentration, decreased haptoglobin level, and negative Coombs test, in various combinations.

Recently, Jodele and coworkers [1] have presented new criteria for TA-TMA. In addition to the central elements of the previous definitions, schistocytes, LDH, thrombocytopenia and anemia/red cell transfusion need, two new criteria have been added: proteinuria/hypertension and the soluble complement factor C5b-9. Table 1 shows the diagnostic criteria by Jodele et al. Five or more of the listed TA-TMA-associated markers indicate a severe disease [8]. An important finding was that some of these signs, proteinuria, hypertension and LDH increase, manifest early and can be used to predict the development of advanced TA-TMA. If proteinuria and an increased level of sC5b-9 concentration are observed, there is a great risk of poor outcome, indicating the need for aggressive treatment.

Table 1. Diagnostic criteria for TA-TMA by Jodele et al [8]

The diagnosis of TA-TMA may be established by: • microangiopathy diagnosed on tissue biopsy, or • laboratory or clinical markers
Laboratory or clinical markers: • Lactate dehydrogenase above the upper limit of normal for age • Proteinuria; a random urinanalysis protein concentration of ≥30 mg/dL • Hypertension; <18 years of age: a blood pressure at the 95th percentile value for age, sex, and height; ≥18 years of age: a blood pressure ≥140/90 mmHg • *De novo* thrombocytopenia; thrombocytopenia with a platelet count <50×10^9/L, or a ≥ 50% decrease in the platelet count • *De novo* anemia; a hemoglobin under the lower limit of normal for age or anemia requiring transfusion support • Evidence of microagiopathy; the presence of schistocytes in the peripheral blood or histological evidence of microangiopathy on a tissue specimen • Terminal complement activation; elevated plasma concentration of sC5b-9 above upper normal laboratory limit

Some clinical and morphological practices in the diagnosis of transplant-associated microangiopathy should be standardized, particularly schistocyte counts. A study was recently performed on behalf of the Transplant Complications Working Party of the EBMT on this issue [9]. A questionnaire of the diagnostic methods of TA-TMA was sent to clinicians and morphologists. Also, sets of blood slides from 10 patients with TA-TMA and from 10 controls were distributed among the transplant centers, and the morphologists were asked to assess the slides as to the presence and proportion of schistocytes.

The survey showed that the International Working Group criteria and the "Overall TA-TMA" criteria were used by 41% of the centers each, in 18% of the centers the diagnosis was made individually by the physician. Interestingly, the interpretation of the percentage of schistocytes varied greatly. This was mainly based on differences in institutional practices, caused by different morphological criteria for schistocytes at different laboratories leading to substantial differences in the interpretation of the presence and degree of schistocytosis (Fig. 1). There is a number of different morphological forms of schistocytes, and the centers differ in which types of abnormal erythrocytes are counted as schistocytes.

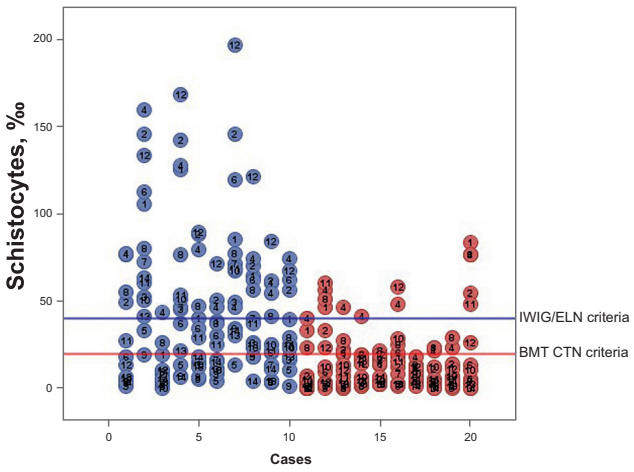

Figure 1. Variability of the schistocyte counts in blood smears of 10 patients with TA-TMA (blue circles) and 10 control patients (red circles) reported by different transplant centers [9]

Role of Complement in TA-TMA

In a proportion of TA-TMA patients the complement cascade has been shown to become activated resulting in the formation of the membrane attack complex and endothelial injury [10]. This is probably caused by inherited or acquired defects in the complement regulatory system, becoming apparent in HSCT-induced stress conditions [10]. Associations between TA-TMA and certain complement-related gene variants have been demonstrated. Complement regulators, gene variants of which have been suggested to be implicated in the pathophysiology of TA-TMA include complement factor H (CFH), complement factor I (CFI), thrombomodulin (THBD), CD46 or membrane cofactor protein (MCP), and CD55. Similarly, complement activators, with gene variants implicated, include complement factor B (CFB), C3, and C5 [2].

The role of complement-activating mechanisms in TA-TMA suggests wider application of complement-inhibiting treatments, especially anti-complement antibodies in the management of this complication.

Treatment of TA-TMA

The treatment of TA-TMA has been difficult and the outcome of severe cases poor. The discontinuation or dose reduction of possibly causative agents, such as cyclosporine, tacrolimus or sirolimus is a general policy, although the documentation of the efficacy of this approach is not completely

solid [8]. Therapeutic plasma exchange is usually not effective in TA-TMA and its use has been discouraged in many reports, but this treatment may be indicated in some cases to remove mutated complement, antibodies against complement, or other triggering factors for endothelial dysfunction [11].

Defibrotide has been occasionally used for the treatment of TA-TMA since many years. More recent studies have reported encouraging results, approximately half or more of the patients with a severe TA-TMA responding without any major adverse effects documented [12, 13, 14]. Other agents including rituximab, daclizumab, etanercept, infliximab, and bosentan have been used without major success [3]. With the increasing understanding of the role of complement in the pathophysiology of TA-TMA, the possible use of complement-inhibiting treatments, especially anti-complement antibodies has recently been a topic of great interest. Most of the clinical experience is with equlizumab.

Equlizumab is a humanized monoclonal antibody. It is a C5 inhibitor and prevents the formation of the membrane attack complex (C5b-9) [15, 16]. The dosing schedule is not well established. Marked individual variation has been documented in the pharmacokinetics, and monitoring the concentrations to confirm adequate dosing may be indicated [8]. Equlizumab treatment can be discontinued after the resolution of TA-TMA, usually without relapse of this complication [3]. The treatment causes increased susceptibility to infections caused by encapsulated bacteria, but this problem may be ameliorated by adequate antibiotic prophylaxis [17]. The cost of this treatment is substantial, and its availability is limited in many countries.

Most of the experience of equlizumab treatment is from pediatric studies. Jodele [10] treated 50 pediatric patients with TA-TMA and multiorgan dysfunction. Seventy-two per cent of the patients survived, compared to less than 10% among historical controls. Bohl et al [13] treated 15 adult patients. The response rate was 93%, but only 33% finally survived. Vasu et al [18] treated 5 adult patients. Three of them recovered while two died of sepsis.

Several other complement inhibitors, targeting components of the classical, lectin or alternate pathway, are under development and are likely to affect the treatment scene in the next few years [3].

Conclusion

TA-TMA remains a challenging complication of HSCT, leading to increased morbidity and mortality. The understanding of the pathophysiology is increasing and may lead to improvements in the diagnostics. Aims at standardizing the criteria of this complication are important especially for study purposes. The therapy is improving, particularly due to the introduction of complement inhibitors. However, the indications and policy of administration of these drugs are not well established and need further study.

Conflict of interest

No conflicts of interest are reported.

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Современные разработки в области трансплант-ассоциированной тромботической микроангиопатии

Тапани Рууту

Клинический исследовательский институт, Университетский госпиталь Хельсинки, Финляндия

Резюме

Трансплант-ассоциированная тромботическая микроангиопатия (ТА-ТМА) является сравнительно частым осложнением трансплантации гемопоэтических стволовых клеток (ТГСК). Ее патогенез весьма сложен, а центральным звеном является повреждение эндотелия. Все больше выясняется роль активации комплемента в патофизиологии процесса. Диагностические процедуры и интерпретация результатов существенно различаются между клиническими центрами, и здесь важны задачи стандартизации критериев диагностики этого осложнения особенно в исследовательских целях. Происходит совершенствование терапии, главным образом, благодаря применению ингибиторов комплемента. Однако показания и тактика назначения этих препаратов еще недостаточно установилась и требует дальнейшего изучения.

Ключевые слова

Трансплантация гемопоэтических клеток, тромботическая микроангиопатия, диагностические методы, стандартизация, терапия, ингибиторы комплемента.